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By _____
Austin Player

AMENDMENT UNDER 37 CFR 1.116
EXPEDITED PROCEDURE -
EXAMINING GROUP 1804

#39

PATENT

Attorney Docket No. 016243-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
Richard H. Tullis	Examiner: J. Martinell
Serial No.: 08/078,768	AMENDMENT UNDER 37 CFR 1.116 EXPEDITED PROCEDURE - EXAMINING GROUP 1804
Filed: June 16, 1993	
For: OLIGONUCLEOTIDE THERAPEUTIC AGENT AND METHODS OF MAKING SAME	

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Asst. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The following remarks are in response to the Advisory Action dated May 4, 1995, and a telephonic interview of July 19, 1995. A Notice of Appeal was filed on April 28 and the Appellant's Brief is due on July 28, 1995. A Petition for a two-month extension of time, until August 28, 1995, is submitted herewith.

Applicant gratefully acknowledges the Examiner's understanding with regard to continued submissions after a Final Office Action has been mailed. As discussed at length during the interview, applicant has diligently tried to address all the outstanding §112 issues, and believes that the Examiner may have overlooked certain aspects of applicant's last two responses. At this time, the applicant requests that the Examiner reconsider his position regarding claim 71 in view of specific statements by the declarants regarding the state of the art in 1981.

REMARKS

Claims 64-72 are pending. The entirety of these remarks relate to claim 71. Unlike the other pending claims, claim 71 is directed to modified, nuclease resistant nucleic acid, and the issues are less complicated than for the claims which encompass unprotected nucleic acid.

In the outstanding Advisory Action the Examiner clarified his remaining basis for rejection of the pending claims which included claim 71. He states:

> Reference to the Office Action mailed December 16, 1992 reveals the actual issue, which is that the instant application fails to guide those of skill in the art as to which oligodeoxyribonucleotides to use.

The Examiner than states that the applicant's previous response was "most unconvincing" because it merely explained that the oligonucleotides existed and failed to show "how to use them" and "fails to even mention the different forms of oligodeoxyribonucleotides in any specific manner."

In the December 16, 1992, Office Action, the Examiner gave three specific reasons why he believed the claims failed to satisfy §112. The reasons focused on whether it was apparent: (a) that the particular oligodeoxynucleotides of any of the references were able to get into the cells; (b) that the particular oligonucleotides were able to hybridize effectively and specifically to a nucleic acid of interest; and, (c) that any particular oligodeoxynucleotides of any of the references were sufficiently stable *in vivo*.

Considering the Examiner's comments in the Advisory Action and in the Office Action of December 16, 1992, there appear to be five remaining §112 concerns. They are the need to: (1) establish that one of skill in 1981 would know which oligonucleotides were resistant to degradation; (2) establish that there was no undue experimentation regarding how to use the modified oligonucleotides; (3) establish that modified oligonucleotides will enter cells; (4) establish that modified oligonucleotides will bind specifically to target oligonucleotides; and, (5) establish that the stability of the modified oligonucleotides is sufficient to achieve the claimed results. In the applicant's April 17, 1995, submission, he responds to the two concerns set forth in the Examiner's Interview of March 13, 1995. These concerns are points 1 and 2. It was not clear to applicant that the latter three points were still at issue, and the Examiner's patience is appreciated. It is believed that the record adequately addresses each of these five points. In the following remarks, the applicant will direct the Examiner's attention to references or portions

of the record where these issues were addressed and asks the Examiner to provide applicant with specific reasons why he believes that the concerns are still at issue. At a minimum, it is expected that some of the five concerns will be resolved and that the record will be clarified for appeal and greatly simplified.

POINT 1: WHICH MODIFIED OLIGONUCLEOTIDES WOULD BE USEFUL.

As filed, the specification teaches that both modified and unprotected nucleic acid can be used in the invention. The modified nucleic acid is exemplified by a phosphotriester form. The specification at page 4, lines 9-13, illustrates this teaching:

> The preferred oligonucleotide has a minimum of about fourteen or more bases, such as about twenty-three bases, and for increased stability, may be transformed to a more stable form, such as a phosphotriester form, to inhibit degradation during use.

The original claims track this teaching. According to claim 1, the compositions of this invention are oligonucleotides. In the dependent claims, the inventor claims oligonucleotides that are preferably transformed into a more "stable form to inhibit degradation" by the host organism (claims 2, 29, 40, 45 and 49) and are preferably a "phosphotriester form" (claims 3 and 30). Clearly, the specification generally suggests the use of stabilized, nuclease resistant oligonucleotides and provides a single example.

For purposes of claim 71, the question is whether the specification adequately directs the reader to alternative, modified oligonucleotides without specifically identifying them.

In section (A)(1) of the two declarations filed on April 14, 1995, each declarant identified five academic references which are representative of the state of the art in 1981 with regard to nuclease resistant oligonucleotides. In section (A)(2) the declarants provided multiple objective reasons why they, as persons of skill in 1981, would have understood the specification to be referring to a specific body of knowledge relating to nuclease resistant nucleic acids. In the declarations the following is stated:

From pages 4-5 of the Schwartz and Ruth Rule 132 declarations filed on April 14, 1995

2. It is my understanding that the Examiner was concerned that the specification as filed would not have suggested that the nucleotide analogs described in the above references were useful in the invention. There are several objective reasons, why those of skill in 1981 would have understood that the text of the specification, i.e., page 4, lines 8-13 and claims 29-33 of the original specification was referring to the above identified body of knowledge.

The above referenced text of the applicant's disclosure states:

> The preferred oligonucleotide ... , for increased stability, may be transformed into a more stable form, such as a phosphotriester form, to inhibit degradation during use.

Original claims 29 and 32 recite stable forms of oligonucleotides that inhibit degradation by organisms and claims 30 and 33 recite phosphotriester forms. The applicant clearly is teaching that stable, nuclease resistant forms of nucleic acid which can duplex to target nucleic acid are preferred forms of the oligonucleotides useful in the invention. Even presuming that those of skill were unaware of the above body of knowledge, to the best of my knowledge, there was no other body of knowledge to which the applicant could have been referring.

Having explained that there was no other body of knowledge that might have been confused with the above reference body of knowledge, it is simply a matter of establishing that one of skill would had the skill to locate the above references. The above references are representative of a significant body of work involving stabilized nucleic acids for understanding enzyme mechanics, transcription studies, for evaluating cellular uptake of nucleic acid and for medical uses. For the Examiner to maintain that those of skill would not have known of the above references or not have been able to find the above references is contrary to the way scientists work and contrary to my understanding of how the Patent Office establishes obviousness. The phosphotriester reference in the original application would have lead one of skill directly to Dr. Paul Miller's work and thus to other analogs. Dr. Miller's published work involved both phosphotriester and phosphonates analogs. Anyone familiar with Dr. Miller's work would have known of analogous work by Dr. Fritz Eckstein using thio-substituted nucleic acid. Even undergraduates were being taught in 1981 that methylation was a key modification to nucleic acid for the purpose of increasing its half-life. In addition, the Examiner is asked to review the work of Dr. Summerton in 1978. This reference is already of record (A33). At page 89, Dr. Summerton summarized the art of modified nucleic acids for inhibiting viral replication and specifically addressed degradation problems. Among the modified nucleic acids taught by Summerton as useful as *in vivo* antiviral agents were the methylated oligonucleotides, thio-substituted nucleic acids as well as the modified oligonucleotides of Miller.

In summary, the above statement provides **six objective reasons** why the declarants believe that the specification was enabling for alternative nuclease resistant analogs. **The six objective reasons are:**

(1) That there was no body of knowledge relating to nuclease resistant nucleic acid which would *not* function in the invention and would confuse those of skill;

(2) That a general teaching in the specification to nuclease resistant nucleic acids and the example to Miller's work was sufficient teaching to suggest all of Miller's related work on modified nucleic acids;

(3) That anyone familiar with Miller's work would also have known about Eckstein's work with modified nucleic acids;

(4) That those of skill in science have the ability to conduct literature surveys;

(5) That Dr. Summerton's 1978 work (A28) expressly summarized the relevant body of knowledge concerning modified oligonucleotides; and,

(6) That two declarants are of the opinion that they would have understood the specification to refer to the various modified nuclease resistant nucleic acid analogs available in 1981.

The Examiner has not responded to these objective statements by the declarants. To clarify the record, applicant respectfully asks the Examiner to comment on any apparent deficiency in the declarant's position. Specifically, the applicant asks why the Examiner maintains that one of skill, after reading the specification in 1981, would not have understood which other modified, stabilized oligonucleotides could have been substituted for the phosphotriesters.

In applicant's view, the inventive aspect of the claims does not involve the choice of any particular degradation resistant oligonucleotide analogs. These analogs were known and were considered as essentially equivalent once the real discovery was presented. The real discovery was the availability of the coding region of mRNA to downregulation and the need to use oligonucleotides of greater length than taught by the prior art when targeting non-coding regions of mRNA.

The decisional law controlling the above issue is clear. Patent applicants need not describe what is already known. In view of the above comments, the applicant respectfully requests reconsideration of this point and clarification if point one is maintained as support for the §112 rejection.

POINT 2: WHICH MODIFIED OLIGONUCLEOTIDES TO USE.

In the Examiner's comments on May 4, 1995, he states, "the applicant's arguments ... are most unconvincing in the absence of a mention or teaching in the application as to how to use them [oligonucleotides]." Applicant offers three responses to point 2. First, the methods for using the different stabilized oligonucleotides are essentially identical to the methods for using the unprotected and the phosphothioester forms of nucleic acids. If the teachings of the specification were adequate for the issuance of the related U.S. Patent No. 5,023,243, they should be adequate for claim 71 once the Examiner is persuaded that the requirements of §112 are otherwise satisfied. One simply floods the external environment of the target cells with sufficient amounts of nucleic acid until you obtain a downregulation of the target protein. The key to using the invention is in the use of a specific length oligonucleotide, not in how you physically expose it to the cells.

Secondly, the declarants, in Section D of their declarations filed on April 14, describe in detail why there is no undue experimentation in simply bathing target cells with the degradation resistant nucleic acid.

The declarants state:

From pages 7-8 of the Schwartz and Ruth Declarations mailed April 14, 1995:

D. THERE IS NO UNDUE EXPERIMENTATION INVOLVED IN THE ADMINISTRATION OF ANTISENSE OLIGONUCLEOTIDES.

The level of skill of those in the art of antisense technology is quite high. Most of the artisans are like myself and hold doctorates in a relevant biological science. To achieve a measurable downregulation of protein expression, one need only contact the target cells with an adequate amount of antisense oligonucleotides. The infusion techniques are conventional and were fully known in 1981. The technique is merely the injection of a saline solution containing the antisense oligonucleotides into the appropriate organ. There is simply no basis to conclude that such a experimental step was anything but routine and intuitively apparent to those of skill.

The Examiner states that the specification failed to teach how to use the specific analogs. While there may be no express teaching of specific analogs to use other than the phosphotriesters, applicant believes that the specification generically teaches that protected and unprotected oligonucleotides can be used; and, that beyond specifying an adequate length, there is no other teaching needed to practice the invention. The technology is just too simple. If the Examiner believes there to be some complexity to this invention, which is not apparent to the applicant, he is asked to state the complexity and applicant will respond with specificity.

Third, in the event the Examiner is not concerned with "how to use" but with "which analog to use," applicant would respond that all the conventional analogs would work. There is no reason to believe that any of the prior art nucleic acid analogs would not work to some degree to downregulate protein provided the appropriate length was used. Each of the analogs described in the five references described by the declarants has been demonstrated to bind specifically to nucleic acid. While it might be possible to deliberately design a nucleic acid analog that is nuclease resistant and unable to bind to a complementary nucleic acid, such an analog would represent an obvious non-working embodiment. The field of pursuit represented by the five references describing different analogs is clearly focused on *maintaining* hybridization specificity while increasing stability against nuclease

activity. In summary, there is no issue regarding which analog to choose. **They should all work.** If the Examiner has objective, scientific reasons why particular analogs might not work, he is respectfully asked to place them into the record and applicant will respond.

POINT 3: WHICH MODIFIED OLIGONUCLEOTIDES WILL ENTER CELLS.

In the Office Action dated December 16, 1992, the Examiner was concerned that it would require undue experimentation to determine which of the possible analogs would enter a cell. Applicant mistakenly believed that this issue was withdrawn. This issue was addressed by the applicant in his remarks submitted on August 29, 1994, in the paragraph bridging pages 6-7, and by the declarants in their declarations submitted in August of 1994 at section (5)(C).

Applicant stated:

Finally, the Examiner raises the issue of cell uptake of nucleic acid. He comments that there are no data and methods for actually "getting short DNAs or RNAs into cells." As explained by the declarants, cells are quite amenable to internalizing short nucleic acid and nucleic acid analogs. There is nothing to teach. Normal cells naturally internalize these compounds. In fact the very literature relied upon by the Examiner to support his obviousness rejection teaches this fundamental fact. For example the Miller reference involves the effect of a trinucleotide analogue on mammalian cells and the Summerton reference discloses at pages 93-94 the routine uptake by animal cells of both RNA and DNA. At page 93, Summerton refers to a paper by Zamecnik and Stephenson (1978). This paper is already of record and applicant would like the Examiner to note that the authors acknowledge in the their paper that the DNA used in the study was analyzed by Dr. Dennis Schwartz, whose Rule 132 declaration is before the Examiner. If the Examiner is aware of facts to the contrary regarding the nature of cellular uptake of nucleic acid he should set them forth with particularity and support his reasons with references or an affidavit.

Declarants stated:

C. **Cell Uptake of Nucleic Acid**

Finally the Examiner raised the issue of cell uptake of nucleic acid. He comments that there are no data and methods for actually "getting short DNAs or RNAs into cells." Living cells have a natural capacity for internalizing short nucleic acids. There is nothing to teach. The cells internalize these compounds without special culture conditions. There is no need to render the cells porous. The literature relied upon by the Examiner to support his obviousness rejection teaches this fundamental fact. For example, the Miller reference involves the effect of a trinucleotide analog on mammalian cells and the Summerton reference discloses at pages 93-94 the routine uptake by animal cells of both RNA and DNA. Finally there is the paper by Zamecnik and Stephenson (1978) which describes the internalization of viral infected cells by a DNA of 13 nucleotides.

If the concern over cellular uptake resurfaced with regard to analogs, applicant asks the Examiner to note the five references cited by the declarants as evidence of the availability of stabilized oligonucleotides in 1981. In four of the five references, the authors report that their stabilized oligonucleotides are internalized by cells.[1]

The Examiner is respectfully asked to reconsider in view of the specific comments set forth above. If point 3 is to be maintained as a basis for supporting the §112 rejection, the Examiner is respectfully requested to provide express reasoning in view of the above remarks.

POINT 4: WHICH MODIFIED OLIGONUCLEOTIDES WILL BIND SPECIFICALLY TO TARGET OLIGONUCLEOTIDES.

Applicant erroneously thought that this concern was no longer at issue. In many of the references that were used by the Examiner to support the §103 rejection, the authors used modified, stabilized nucleic acids for binding to specific targets. There is simply no scientific reason to presume that the various

[1] The Miller 1977 (A1) reference entitled, "Effects of a Trinucleotide Ethyl Phosphotriester, $G^{m}p(Et)G^{m}p(ET)U$, on Mammalian Cells in Culture," describes a 1974 reference (A9) in which the triester forms were synthesized.

modified nucleic acids known in 1981 would not have the ability to hybridize to their complementary targets. For example, Miller's work with phosphonate analogs described their use to specifically bind intracellularly to initiation codons and tRNA binding sites of mRNA. The Kunkel reference (Exhibit 1 of the April 14, 1995, declarations) details the use of their thiophosphate analogs as template for making DNA, and specifically acknowledges the base pairing specificity of the analogs during synthesis (see the bridging paragraph between pages 6735-6756 where the authors state:

> ...the analogue is not mutagenic by any unexpected mechanisms, such as a change in base-pairing specificity.

The declarants also state, in the bridging paragraph between pages 4 and 5 of their April 14, 1995, declarations, that in 1981, undergraduates were being taught that methylation of nucleic acid was a key modification to nucleic acid for the purpose of increasing its half-life. The declarants were referring to the natural methylation of bases by cells to stabilize the turnover of mRNA. If the Examiner is not familiar with this fact and it is determinative of patentability, applicant will submit a declaration to this effect. The Befort reference using artificially methylated nucleic acid to inhibit viral replication is an extension of this knowledge.

Finally, the Summerton reference (1978) details the state of the art of nucleic acid analogs with regard to anticancer and antiviral agents. In the first two sentences of this section, Dr. Summerton clearly states that analogs and derivatives of nucleic acids are functioning because of specific base pairing. He states at page 89:

> ...there are a growing number of reports on antiviral and/or anticancer activity of homopolyribonucleotides, analogs, and derivatives thereof, and a synthetic oligodeoxy-ribonucleotide. The general rationale for this work is that the introduction of such polymers into virally infected cells may lead to pairing between the introduced polymer and a specific viral structure of nucleotide sequence. Presumably such pairing would inhibit some critical function in the virus life cycle.

The declarants have provided objective reasons why those of skill would view the available nucleic acid analogs as equivalents to the

phosphothioesters with regard to their ability to specifically hybridize to targets. In view of these objective reasons, the applicant respectfully asks that the Examiner provide objective reasons why he believes it would require undue experimentation to identify analogs from the literature that would not be operable in the invention due to their inability to hybridize.

As discussed during the telephonic interview, most of the literature describing analogs is focused on modifications to the phosphate backbones, or to limited methylation of specific bases. If one were to modify the nucleotide bases to the degree that specific hybridization was no longer possible, the analogs would be biologically inactive, and it is unlikely that such useless analogs would be even reported in the peer reviewed literature.

POINT 5: STABILITY OF SPECIFIC OLIGONUCLEOTIDES.

The Examiner, in 1992, raised the question whether the references before him at that time suggested that specific analogs would have adequate stability *in vivo*. The particular references before the Examiner were Exhibits A-F. A number of these references were published after the priority filing date in 1981 of the instant application. In contrast, declarants presented in their April 14, 1995, submission, five academic references that were published before the effective priority date and taught that various nucleotide analogs were biologically active under intracellular conditions.

Applicant believed that this issue was outstanding for the unprotected oligonucleotides, but that claim 71 was free of this concern. At present, applicant is vigorously pursuing the claims embracing unprotected nucleic acid asserting that the stability is sufficient for observing biological effect, although the commercial importance might be less than for the stabilized oligonucleotides. However, it is not clear why the Examiner doubts the truth of the allegation that stabilized oligonucleotides would not be adequately stable to work, especially in view of the objective evidence establishing that unprotected nucleic acid is sufficiently stable when directly injected into animals.

CONCLUSION:

Applicant appreciates the opportunity to clarify the record. The Examiner is respectfully asked to reconsider each of the above five points, and, if appropriate, withdraw those concerns which he believes to be adequately traversed. If there are any remaining issues, the Examiner is asked to identify them and to provide objective, scientific reasons why the present record does not convince him that one of skill could not have practiced the invention using stabilized nucleic acid other than the phosphothioester analogs.

During the interview, applicant has previously offered to consider limiting all the pending claims to stabilized nucleic acids. If the Examiner is considering claim allowance, he is asked to review these claims in view of U.S. Patent No. 5,023,243. Applicant's attorney has reviewed the multiple files in this family of applications, and those files do not reveal that a terminal disclaimer was filed by applicant's assignee. The Examiner is respectfully requested to consider whether he considers the pending claims to be patentably distinct over '243 in view of §103.

If the Examiner believes that a telephone interview would clarify any remaining issues or expedite prosecution, he is invited to call the undersigned attorney at the number provided below.

Respectfully submitted,

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